REMARKS/ARGUMENTS

Claims 35, 37, 38, 40-43, 48, 49, 52 and 53 are pending. Claims 35, 37, 38, 40, 43, 43, 48, 49 and 53 stand rejected. Claims 41 and 52 are objected to and would be allowable if written in independent form.

Applicants acknowledge withdrawal of previous rejections of claims 35, 37-43, 48, 49 and 52 under 35 U.S.C. § 112, second paragraph; of claim 53 under 35 U.S.C. § 103(a) over Desjarlais *et al.*; and of claims 35, 37, 38, 40, 42, 43, 48, 49 and 53 under 35 U.S.C. § 103(a) over Choo *et al.* (1994b) in view of Choo *et al.* (1994a).

Claims 35, 40, 48, 49 and 53 stand newly rejected as obvious over Choo (1994b), in view of Choo (1994a) in view of Corbi. Choo (1994b) is cited as discussing a method of designing a zinc finger protein that binds to a BCR-ABL target site. The Examiner acknowledges that Choo (1994b) does not show three finger zinc finger proteins, computer based methods or a database in which zinc finger proteins have a third finger different from at least one third finger of another protein in the database. Choo (1994a) is cited as disclosing screening a phage display library in which the middle of three zinc fingers is randomized. Corbi is cited as disclosing a zinc finger protein termed Mago (Figs. 1-2), and a target binding site (Fig. 3). The third finger of Corbi's protein is said to be different from that of Choo (1994b). The Examiner takes the view that it would have been obvious to precharacterize the selected random library members of Choo (1994b) and to record such characterizations in a database as allegedly shown in Choo (1994a) Fig. 2. The Examiner also takes the view that it would have been obvious to automate the generation and use of the database by use of computers because it is obvious to automate a process. The Examiner further alleges it would have been obvious to add further zinc finger proteins such as the Mago protein of Corbi[1] to increase further the diversity of choices because zinc finger proteins designed in Choo (1994b) had variability in their affinity and subsequent screening was required. This rejection is respectfully traversed.

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[1] Although the Office Action does not state what the protein of Corbi *et al.* would be added to, Applicants assume that the Examiner is suggesting that it would have been obvious to add the protein disclosed by Corbi *et al.* to the database of zinc fingers allegedly disclosed by Choo *et al.* (1994a)

The proposed motivation of increasing diversity of choices would not have motivated combination of Corbi with Choo (1994b). The goal of Choo (1994b), as the Examiner recognizes, was to design a zinc finger protein to a specific target sequence that spans the Bcr-Abl junction (i.e., (5'GCA GAA GCC3'). By contrast, Corbi's protein was designed to bind to the target ATG TGG GTT (see Fig. 3). There is no apparent similarity between Corbi's target and that of Choo (1994b). Therefore, the zinc finger components of Corbi's zinc finger protein would not bind to the triplets of Choo (1994b), and would be of no apparent use in Choo (1994b)'s goal of designing a zinc finger protein to bind to the Bcr-Abl target. No other goal is disclosed or suggested by Choo (1994b).[2]

Further, the proposed manner of combination of Choo (1994b) with Choo (1994a) does not result in a database comprising designations for a plurality of zinc finger proteins, subdesignations for each of three fingers for each zinc finger protein, and their corresponding target nucleic acid sequences, as specified in claim 35. The tables shown in Figs. 2 of the respective references suffer from similar deficiencies in that both provide designations for only a single finger of a zinc finger protein and neither presents a target sequence with three triplets. Although the physical zinc finger proteins described in the cited references may inherently have had three zinc fingers, these physical proteins are not components of a database. If Fig. 2 of either Choo reference is viewed as a database, then the database is composed of the typewritten data in the tables. These typewritten data do not expressly or inherently contain designations of zinc finger proteins, subdesignations of each of three fingers for each zinc finger protein, or the target sequences of the zinc finger proteins, as claimed.

Moreover, with respect to claims 48, 49 and 53, the Examiner's allegation that automation of a process by use of a computer is obvious assumes the references disclose a procedure capable of being automated. In Choo (1994b), the goal was to design a zinc finger protein to a specific target sequence and every sequence in Fig. 2 was already known to bind to one of the triplets in that target sequence. Fig. 2 already indicates which sequences bind to

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[2] Moreover, there would have been no motivation to combine Corbi's three-finger protein with Choo's listings of individual zinc fingers (see below).

which triplet of the intended target sequence. It is not apparent how any processing of the data in a computer could make the data in Fig. 2 any clearer or more useful for designing a zinc finger protein to bind to Choo(1994b)'s intended target sequence. Thus, it would not have been obvious to use a computer to process the data in Fig. 2 of Choo 1994(b). Likewise, Choo (1994a) does not disclose any use of the data in Fig. 2 susceptible to automation. Fig. 2 is merely a compilation of data obtained from a particular experiment. Without identification of a process that could benefit from computerized automation, it would not have been obvious to employ a computer, as claimed.

For these reasons, it is submitted that a prima facie case of obviousness has not been established and the rejection should be withdrawn.

Claims 35, 37, 38, 40, 42, 43, 48, 49 and 53 stand rejected as obvious over Choo (1994b) in view of Choo (1994a) in further view of Isalan. Choo (1994a) and Choo (1994b) are cited as above. Isalan is cited as showing two variants of zinc finger libraries of Choo (1994a) in which the second and third fingers contain variant sequences. The Examiner alleges that the target binding site of the library members is shown in Fig. 3. The Examiner also alleges that Isalan shows that the context of neighboring fingers affects the target site specificity of a zinc finger. The Examiner takes the view that it would have been obvious to precharacterize the selected random library members of Choo (1994b) to any desired extent, and to record such characterizations in a database as allegedly shown in Choo (1994a). The Examiner also alleges it would have been obvious to use computers because it is obvious to automate a process. The Examiner further alleges it would have been obvious to use libraries in which multiple fingers including the third finger were randomized so that zinc finger neighbor context was varied in view of Isalan's teaching that randomization of neighboring fingers allows for increased diversity of binding site specificity in individual zinc fingers. The Examiner also alleges that it would have been obvious to maintain correspondence between zinc finger positions in a database of zinc finger proteins and the position of the zinc finger in a designed zinc finger protein because Isalan shows that the identity of neighboring zinc fingers affects the specificity of a zinc finger. This rejection is respectfully traversed.

The previous comments regarding the proposed manner of combination of Choo (1994b) with Choo (1994a) not resulting in a database comprising designations for a plurality of zinc finger proteins, subdesignations for each of the fingers of each zinc finger protein, and a corresponding target nucleic acid sequences for each zinc finger protein in the database are equally applicable to the above rejection. As noted, insofar as Figs. 2 of Choo (1994b) and (1994a) are regarded as being databases, they are databases of only a single finger of zinc finger protein. Fig. 3 of Isalan shows amino acid sequence for only one and a fraction fingers, and target sequences of only two nucleotides. Although the physical zinc finger proteins described in the cited references may inherently have had three zinc fingers and the target sequence may have had three triplets, these physical proteins and target sequence are not components of a database. If Fig. 2 of either Choo reference or Fig. 3 of Isalan is viewed as a database, then the database is composed of the typewritten data in the Figures. These typewritten data do not expressly or inherently contain designations of zinc finger proteins, subdesignations of each of three fingers for each zinc finger protein, or the target sequences of the zinc finger proteins, as claimed.

Further, the proposed motivation of increasing diversity of choices would not have motivated combination of Isalan with Choo (1994b). The goal of Choo (1994b) was to design a zinc finger protein to a specific target sequence that spans the Bcr-Abl junction (i.e., (5'GCA GAA GCC3'). By contrast, the zinc finger proteins of Isalan were selected to bind to target sequences of the form 5'GNX XCG GCG 3' or 5' GCX XCG GCG 3'. At most, only the third finger of some of Isalan's proteins would bind to a triplet present in Choo (1994b)'s target sequence. However, Isalan's selection strategy was to co-randomize and select the third and second fingers simultaneously. Thus, Isalan's third fingers were always co-selected with neighboring second fingers that would not have the appropriate specificity to bind to Choo (1994b)'s target sequence. One would not have been motivated to separate Isalan's third fingers from the neighboring second fingers with which they were co-selected because to do so would effectively nullify the purpose of the co-selection. One also could not use a combination of Isalan's third and second fingers together with Choo (1994b) fingers, because the second fingers

of Isalan have the wrong target specificity. Therefore, one would not have been motivated to combine Isalan's third fingers with the other zinc fingers shown in Fig. 2 of Choo (1994b).

Moreover, with respect to claims 37, 42 and 43, the references are distinguished for an additional reason, namely, Isalan would not have motivated a design method which uses information on the position of the zinc fingers in the precharacterized zinc finger proteins in the database. Specifically, claim 37 requires a step of identifying subsets of zinc finger protein(s) based on both the binding specificity of a zinc finger and the position in the protein from which the zinc finger binds its triplet subsite. As noted in the specification (see, e.g., p. 29, lines 26-30), such is advantageous because when the environment of each finger in a designed zinc finger protein is analogous to its environment in the precharacterized zinc finger protein in the database, it is likely to bind with similar specificity and affinity in the designed zinc finger protein as it did in the precharacterized protein.

Isalan's observation that the binding specificity of one zinc finger in a zinc finger protein may depend on the identity of its neighboring fingers would not have suggested the claimed methods. Rather, the observation suggests that the artisan do what Isalan himself did to overcome the problem of neighboring fingers, that is randomize and select more than one finger simultaneously:

> [W]e now show that this limitation can be overcome by the concerted randomization of certain amino acid positions in adjacent zinc fingers that specify overlapping DNA subsites. This illustrates an important mechanism underlying DNA recognition by arrays of zinc fingers, and points the way to improved strategies for the design of highly specific zinc finger proteins that bind any given nucleotide sequence.
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> Isalan, at p. 12026 (Abstract)

By teaching the importance of selecting neighboring fingers simultaneously, Isalan effectively teaches away from the claimed methods which result in assembly of individual fingers in a modular fashion without regard to whether the fingers previously existed as neighbors. The presently claimed methods do not seek to preserve sequence context by maintaining a zinc finger in contact with its neighboring zinc finger in a preexisting zinc finger

protein (as in Isalan's solution) but rather to preserve positional context by placing a zinc finger in a designed protein in same position as it occurs in a preexisting protein. Isalan provides no indication that preservation of positional context without sequence context would be beneficial to zinc finger binding specificity. Without such an understanding, the artisan would not have been motivated to combine the teaching of Choo (1994a) and/or (1994b) with Isalan, much less in a way that approximates to the presently claimed methods. Rather, the artisan would have simply done what Isalan did, namely co-randomize adjacent fingers.

The previous comments regarding lack of motivation to use a computer when no process susceptible to automation is disclosed are also equally applicable to the present rejection of claims 48, 49 and 53. Figure 3 of Isalan like Fig. 2 of Choo (1994a) is merely a compilation of experimental data. Neither reference discloses any use of the data susceptible to automation. Further, it is not apparent how a computer could process the data of Fig. 2 of Choo (1994b), as discussed above. In the absence of a process susceptible to automation, it was not obvious to use a computer. Thus, claims 48, 49 and 53 are distinguished on additional grounds.

For these reasons, withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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